Disease-free interval:		
No surgery	2 (1%)	4 (2%)
0-12 months	25 (16%)	22 (13%)
>12-24 months	35 (22%)	30 (18%)
> 24 months	97 (61%)	113 (67%)
Prior surgery for breast cancer:		
Yes	176 (79%)	188 (79%)
No	45 (20%)	49 (21%)
No data	2 (1%)	0
Prior radiotherapy:		
Yes	104 (47%)	108 (46%)
No	117 (53%)	129 (54%)
No data	2 (1%)	0
Prior hormonal therapy:		
Yes	75 (34%)*	79 (33%)**
No	148 (66%)	158 (67%)
Prior adjuvant chemotherapy:		
Yes	45 (20%)	53 (22%)
No	178 (80%)	184 (78%)
Number of organs involved:		
1	68 (31%)	73 (31%)
2	80 (36%)	82 (35%)
3	51 (23%)	53 (22%)
4	15 (7%)	21 (9%)
5	7 (3%)	8 (3%)
No data	2 (1%)	0
Classification of metastases:		
Bone only	19 (9%)	19 (8%)
Soft tissue (ST) only	38 (17%)	49 (21%)
ST + bone	37 (16%)	28 (12%)
ST + viscera	32 (14%)	39 (17%)
ST + viscera + bone	27 (12%)	31 (13%)
Viscera only	40 (18%)	37 (16%)
Viscera + bone	28 (13%)	34 (14%)
No data	2 (1%)	0

* 27 for advanced disease
**42 for advanced disease

Reviewer Comments:

1. More patients on the CMF arm were diagnosed prior to age 50; more patients on the FEC arm at the time of entry were age 60 or older (p=0.009 according to the sponsor). Given the balanced distribution of performance status, disease-free interval, number and sites of metastases, and menopausal status, it is unlikely that this imbalance in age alone significantly affected the study outcome.

2. The reviewer looked at the individual sites of metastases, which were well-balanced between treatment arms.

3. The majority of patients on both arms did not have their tumors assessed for receptor status. Estrogen and progesterone status has not been clearly shown to affect response to chemotherapy and should not affect the endpoints of DFS or response rate. Receptor status may influence prognosis and survival. Randomization should have decreased the chance of an imbalance in this factor.

4. Three patients on FEC and 4 on CMF received 2 lines of hormonal therapy for advanced disease. One patient on FEC and 2 on CMF received 2 lines of hormonal therapy for adjuvant treatment. One patient on CMF received 2 lines of adjuvant chemotherapy. Few patients received more than one prior treatment and their data are unlikely to affect study outcome.

11.9 On-study follow-up

Patient disposition throughout the trial is summarized in the following table:

Table 60. Patient disposition, study HEPI 013 (modified from sponsor's table 5, volume 2.33, page 75)

Disposition	FEC (n=223)	CMF (n=237)	Total (n=460)
Treatment completed per protocol	72 (32%)	71 (30%)	143 (31%)
Progressive disease/relapse	74 (33%)	104 (44%)	178 (39%)
Toxicity	11 (5%)	9 (4%)	20 (4%)
Adverse reaction	1 (0.4%)[1]	0	1 (0.2%)
Cardiac toxicity	15 (7%)	1 (0.4%)	16 (4%)
Patient refusal	28 (13%)[2]	30 (13%)	58 (13%)
Protocol violation	2 (1%)	0	2 (0.4%)
Death on treatment	7 (3%)	9 (4%)	16 (4%)
Lost to follow-up	6 (3%)[3]	5 (2%)	11 (2%)
Other	7 (3%)[4]	8 (3%)[4]	15 (3%)

[1] Pulmonary embolism
[2] 2 patients were never treated
[3] Includes 1 patient who was never treated
[4] 1 patient on each arm was never treated

"Other" reasons included medical decision (2 on FEC, 1 on CMF), investigator error (2 on FEC), personal reasons (1 on FEC), change in treating physician (1 on CMF), stable disease after 7 cycles (1 on CMF), intercurrent disease (glaucoma in a FEC patient; erysipelas in a CMF patient), failure to return (1 on CMF), surgery followed by progression (CMF), and "new therapy" (CMF patient).

Reviewer Comment:

1. About one-third of patients completed the planned therapy.
2. There was a higher rate of disease progression on CMF than on FEC.
3. Cardiac toxicity was greater with FEC than with CMF; other toxicities/adverse events as a reason for early withdrawal and patient acceptance of therapy were comparable between treatment arms.
4. At the reviewer's request, the sponsor provided the following table and information, which summarizes how many cycles were given, how many were responders, and how long patients were observed.

Four hundred sixty patients were randomized, 223 to FEC and 237 to CMF. Of these patients, 259 (134 on FEC and 125 on CMF) received at least 6 cycles of therapy. Their course is summarized in the following table:

Table 60a. Patients who received at least 6 cycles of therapy (sponsor's amendment 17, May 11, 1999)

Characteristic	FEC (n=134)		CMF (n=125)	
	CR + PR (n=108)	No change (n=23)	CR + PR (n=92)	No change (n=25)
Patients with additional cycles:				
7-8 cycles	26	3[1]	21	2[1]
9 cycles	58	3[1]	49	0
Responders:				
Within 6 cycles	98	NA	84	NA
After C6	10		8	
Follow-up:				
Total with F/U	108	22	91	25
Lost to F/U	0	1	1	0
Mean F/U time	21 months	18 months	19 months	22 months
Patients with PD:	**85**	**21**	**72**	**18**
On therapy	7	7	7	8
Off therapy[2]	78	14	65	10

[1] Patients received additional cycles because some tumor reduction was observed within the 6th cycle
[2] Defined as PD that occurs later than the date of the last cycle (day 1) plus 28 days

The majority of responses occurred during the first 6 cycles. A similar percentage of the responders on each arm received additional cycles, and a similar number of additional cycles. One patient on each arm was lost to follow-up. The mean follow-up time for FEC responders was longer than for CMF responders; the mean follow-up time for patients with no change was longer on CMF than on FEC. Among responders, the percent who progressed on and off therapy was similar between treatment arms. Among those with no change, 44% progressed on therapy on the CMF arm, compared to 33% for the FEC arm. Among patients with no change who progressed off therapy, 67% progressed on the FEC arm and 56% on the CMF arm.

This tabulation indicates that inequities in follow-up are unlikely to account for the reported differences between treatment arms.

11.10 Removal from study, protocol violations

11.10.1 Removal from study

Patients were removed from study for the following reasons:

- Progressive disease
- Dose-limiting cardiomyopathy
  - ➢ Congestive heart failure diagnosed by two or more of the following:
    - Cardiomegaly by CXR
    - Basilar rales
    - S_3 gallop
    - Paroxysmal nocturnal dyspnea and/or orthopnea and/or significant dyspnea on exertion
- MUGA or echo evidence of cardiomyopathy (see section 11.2.3)
- Unacceptable toxicity which precluded further therapy
- Severe intercurrent illness
- Patient refusal
- Physician deems discontinuation in the patient's best interest

In the as-randomized population, 26 patients on FEC (12%) and 30 (13%) on CMF refused further therapy. Five patients on each arm were lost to follow-up.

11.10.2 Protocol violations

One patient (Poland, center 55, number 40) was treated prior to randomization and was excluded from all analyses. She received FEC for 9 cycles with a partial response. Four months after treatment, she progressed and received additional chemotherapy regimens. She was subsequently lost to follow up.

Six patients on FEC and 13 on CMF were considered ineligible (first 7 violations listed below). Other patients were eligible, but had protocol violations.

Table 61. Protocol violations, Study HEPI 013

Violation	FEC (n=223)	CMF (n=237)	Total (n=460)
Treated prior to randomization			1
Wrong diagnosis	0	1	1
No breast cancer	0	5	5
Time since adjuvant chemotherapy or hormonal therapy less than permitted	2	5	7
Laboratory abnormalities	3	0	3
Brain metastases	1	1	2
Concomitant tamoxifen	0	1	1
Randomized but did not receive treatment	4	0	4
Treated with the non-randomized arm	0	2	2
Responders treated with less than 9 cycles	8	5	13
Treated with more cycles than per protocol	0	2	2
Non-compliance	1	0	1

The study report (volume 2.33, 8/24/043) indicates that 6 patients were untreated. On the FEC arm, 2 refused therapy, 1 had a protocol violation, 1 was lost to follow up, and 1 patient was taken off study for other reasons. On the CMF arm, 1 patient was not treated for other reasons. The "other reasons" were the presence of CNS metastases and the decision to see another physician for care.

Among treated patients, 1 patient randomized to FEC was removed because of a protocol violation (type not given).

Reviewer Comment:

1. Listings for the ineligible patients were reviewed.

- Wrong diagnosis, no breast cancer (6 patients):

1 patient had biopsy-proven lung cancer, not breast cancer

3 patients with solitary pulmonary lesions, no biopsy

1 patient with a solitary liver lesion stable for 3 years and an initial stage of $T_1N_0M_0$

1 patient with a solitary lung lesion (no biopsy) and bone lesions

- Abnormal laboratory data

1 patient randomized but not treated because of low platelets and WBC at baseline

1 patient entered on study with the permission of the central office with a platelet count of 89,000 (100,000 required by protocol)

1 patient with a baseline bilirubin of $\geq$ 2 mg/dl; later removed for toxicity

- Time since adjuvant therapy
  4 patients with recurrence < 12 months after adjuvant treatment (3 CMF, 1 FEC)
  1 patient entered the study within 4 months of stopping hormonal therapy
  2 patients received 2 lines of adjuvant hormonal therapy

- Brain metastases
  2 patients had brain metastases diagnosed after randomization (1 patient time not given, 1 patient within 2 weeks)

- Concurrent hormone therapy
  1 patient began treatment within 7 days of stopping tamoxifen. The sponsor felt her response might be attributed to tamoxifen withdrawal effect and considered her ineligible.

2. In section 11.13.1.c, Cardiac toxicity, the reviewer found through a database query that 5 patients (all from the same institution) were entered on study with baseline left ventricular ejection fractions of 30-35%. The sponsor answered that at this institution, normal LVEF values by ECHO were reported to be 30-40%.

3. Few patients had significant protocol violations. The effect of most of these violations would have favored the CMF arm.

11.11 On-study treatment

11.11.1 Dose Intensity

11.11.1.a Actual dose-intensity

The actual dose-intensities delivered in this trial are summarized in the following table:

Table 62. Actual dose-intensity (DI) in $mg/m^2/wk$

Drug	FEC			CMF		
	Planned DI	Mean DI	Median DI	Planned DI	Mean DI	Median DI
5-FU	333.3	240.03	246.41	450	299.03	300.23
Epi/MTX	33.3	24.69	25.11	26.7	20.42	20.52
CTX	266.7	194.95	198.49	333.3	252.62	252.44

11.11.1.b Relative dose-intensity

Relative dose intensities are summarized in the following table:

Table 63. Relative DI in $mg/m^2/wk$

Drug	FEC		CMF	
	Mean DI	Median DI	Mean DI	Median DI
5-FU	0.72	0.74	0.75	0.75
Epi/MTX	0.74	0.75	0.77	0.77
CTX	0.73	0.74	0.76	0.76
All drugs	0.73	0.74	0.76	0.76

Reviewer Comments:

1. The CMF arm had a greater actual DI for 5-FU and cyclophosphamide compared to the FEC arm. The FEC arm delivered a higher DI for epirubicin than did the CMF arm for methotrexate. Any differences in efficacy between treatment arms that favor FEC are likely to be related to epirubicin rather than to an effect of 5-FU and cyclophosphosphamide.

11.11.2 Cumulative dose

The mean cumulative epirubicin dose delivered on FEC was 544.7 mg/m^2 and the median delivered dose was 581.5 mg/m^2. The mean and median cumulative delivered methotrexate doses on CMF were 403.2 and 403.5 mg/m^2. The total dose given per patient is summarized in the following table:

Table 64. Epirubicin or methotrexate total administered dose (Sponsor's table 54, volume 2.33, page 126)

Dose administered (mg/m^2)	FEC (n=220)	CMF (n=234)
1—100	13 (6%)	16 (7%)
100--< 200	16 (7%)	33 (14%)
200--< 300	16 (7%)	27 (12%)
300--< 400	20 (9%)	39 (17%)
400--< 500	24 (11%)	49 (21%)
500--< 600	38 (17%)	18 (8%)
600--< 700	29 (13%)	30 (13%)
700--< 800	16 (7%)	22 (9%)
800--< 900	34 (16%)	0
900--< 1000	14 (6%)	0

Reviewer Comments:

1. The targeted cumulative doses were 600 mg/m^2 for epirubicin and 480 mg/m^2 for methotrexate for all patients. Responders were targeted to receive 900 and 720 mg/m^2 respectively. Sixty percent of patients on FEC received 500 mg/m^2 or more of epirubicin; 51% of patients on CMF received 400 mg/m^2 or more of methotrexate. It is likely that a higher incidence of progressive disease on CMF accounts for this difference.

11.11.3 Treatment cycles

11.11.3.a Number of cycles

The number of cycles administered is summarized in the following table:

Table 65. Maximum number of cycles administered per patient (as randomized)

Maximum no. of cycles	FEC (n=223)	CMF (n=237)	Total (n=460)
None	5 (2%)	1 (0.4%)	6
1	21 (9%)	16 (7%)	37
2	10 (5%)	25 (11%)	34
3	9 (4%)	25 (11%)	34
4	23 (10%)	26 (11%)	48
5	21 (9%)	19 (8%)	40
6	47 (21%)	54 (23%)	101
7	15 (7%)	15 (6%)	30
8	11 (5%)	6 (3%)	17
9	61 (27%)	48 (20%)	109
10	0	2 (1%)	2

The median number of cycles administered in each group was 6. Sixty percent of patients on FEC compared to 53% on CMF received 6 or more cycles of treatment.

11.11.3.b Duration of treatment cycles

The median duration of treatment cycles was 28 days on each arm, when either the first cycle or all cycles were considered.

11.11.3.c Treatment delays

On FEC, 17% of cycles were given every 3 weeks; 62% were given within 4 weeks. Twenty-one percent were given greater than 30 days apart. On CMF, 27% of the cycles were given every 3 weeks, 54% within 4 weeks, and 19% greater than 30 days. On both arms, the most common reason for delay was hematologic toxicity.

Reviewer Comment:

1. Cycle duration did not change appreciably with an increased number of cycles.
2. The percent of cycles with prolonged (>30 day delay) was similar on both arms.
3. More CMF cycles were delivered on time than FEC cycles.
4. More patients on FEC received 6 or more cycles of treatment, suggesting that patients on CMF were more likely to have progressive disease.

11.12 Efficacy results (intent-to-treat analyses)

Although an intent-to-treat analysis was specified, the analyses were performed on evaluable patients. Fifty-seven patients (30 randomized to FEC, 27 randomized to CMF) were considered by the sponsor to be inevaluable.

Reviewer Comments:

1. The narratives for the inevaluable patients (56, not 57 provided) were reviewed and are summarized below.

Patient refusal:

1 patient on CMF; removed after C1 for grade 4 mucositis
1 patient on CMF refused therapy after C1 because of mucositis
1 patient on CMF refused therapy after C1 because of myelosuppression
2 patients refused further CMF after 1 cycle
1 patient refused further CMF after 2 cycles
1 patient refused further CMF after 3 cycles; no tumor evaluation

3 patients refused further treatment after C1 FEC (reason not given)
1 patient refused further treatment after C1 FEC because of mucositis, lung candidiasis, and "FN" (not defined by the sponsor)
1 patient refused further treatment after C3 FEC due to toxicity
1 patient refused further treatment after 3 cycles of FEC; no tumor evaluations

Deaths:

2 patients died of febrile neutropenia after C1 CMF
1 patient died 7 days after C1 CMF
1 patient died of sepsis and bleeding after C2 CMF
1 patient died 16 days after C2 CMF of febrile neutropenia

2 patients died of PE after C1 FEC
1 patient died of sepsis after C2 FEC without a second tumor assessment
1 patient died of PE after C2 FEC without restaging
1 patient died of febrile neutropenia after C2 FEC
1 patient died of PE on FEC

Never treated:

1 patient with brain metastases randomized to CMF; never treated

4 patients randomized to FEC; did not return and were never treated
1 patient randomized to FEC; developed PD prior to treatment

Incomplete assessment:

1 patient on CMF found to have PD in bone; did not have baseline bone evaluation
1 patient incompletely evaluated after 7 cycles CMF
1 patient on CMF did not have all lesions assessed consistently at each timepoint

1 patient received 4 cycles of FEC (D1 treatment only on 3 of them) with no interim assessments after baseline until PD

Disease progression:

1 patient on FEC with PD after C1

1 patient received 1 cycle of FEC; returned 9 weeks later with PD

1 patient received C1D1 FEC and was found to have a bone lesion on C1D2; removed for PD

Noncompliance:

1 patient received C1 and C2D1 CMF and did not return

2 patients received two cycles of CMF and were lost to follow-up

1 patient lost to follow up after 4 cycles of CMF without tumor evaluations

2 patients randomized to FEC was lost to follow-up

Toxicity:

1 patient on CMF taken off study for hepatic toxicity without restaging

1 patient removed for febrile neutropenia after C1 CMF

1 patient off-study for hematologic toxicity after 2 cycles CMF

1 patient received C1 FEC; taken off study for hepatic toxicity

1 patient taken off study after C1 FEC for PE

1 patient removed after 1 cycle of FEC for acute glaucoma

1 patient on FEC taken off study after C1 for sinus tachycardia

1 patient taken off study for severe neutropenia after 2 cycles of FEC

1 patient removed from study after 3 cycles of FEC for cardiotoxicity

1 patient on FEC taken off study for hematologic toxicity

Combined therapy:

1 patient randomized to CMF continued to receive tamoxifen and NSAIDs; died of PD within a few weeks

1 patient randomized to CMF stopped tamoxifen 7 days before study entry. Excluded because of potential tamoxifen withdrawal effects

Protocol violations:

1 patient received up to C3D1 FEC, then taken off study for febrile neutropenia and poor compliance. Considered ineligible because dose reductions were not made

The cases listed above show the problems with analyzing evaluable patients only. Most of these patients had death or toxicity directly related to therapy, even though some were characterized as "patient refusal". In order to avoid bias, all randomized patients should be analyzed on an intent-to-treat basis.

11.12.1 Time to progression

The sponsor evaluated TTP in treated eligible evaluable patients, a total of 189 patients on FEC and 200 on CMF. One hundred fifty-four and 164 events occurred respectively, with median TTP of 266 and 190 days respectively. The p-value (stratified logrank test) was reported to be p=0.0064. The hazard ratio of FEC versus CMF was 0.73 (95% CI 0.59, 0.92), meaning there was a 27% reduction in the risk of progression.

Median TTP was 8.9 months in the FEC arm and 6.3 months in the CMF arm.

A Cox proportional hazards model included the following as significant factors: treatment, number of sites (1-2 versus more than 2) and dominant metastases (visceral vs. non-visceral). The Cox model yielded a hazard ratio of 0.72 (p=0.004). The hazard ratio of FEC:CMF for number of sites (1-2: >2) was 1.7 and for visceral: non-visceral disease was 1.4. Within strata (i.e., visceral compared to non-visceral disease within strata of 1-2 lesions/>2 lesions), the risk of developing progression was consistently lower on FEC than on CMF.

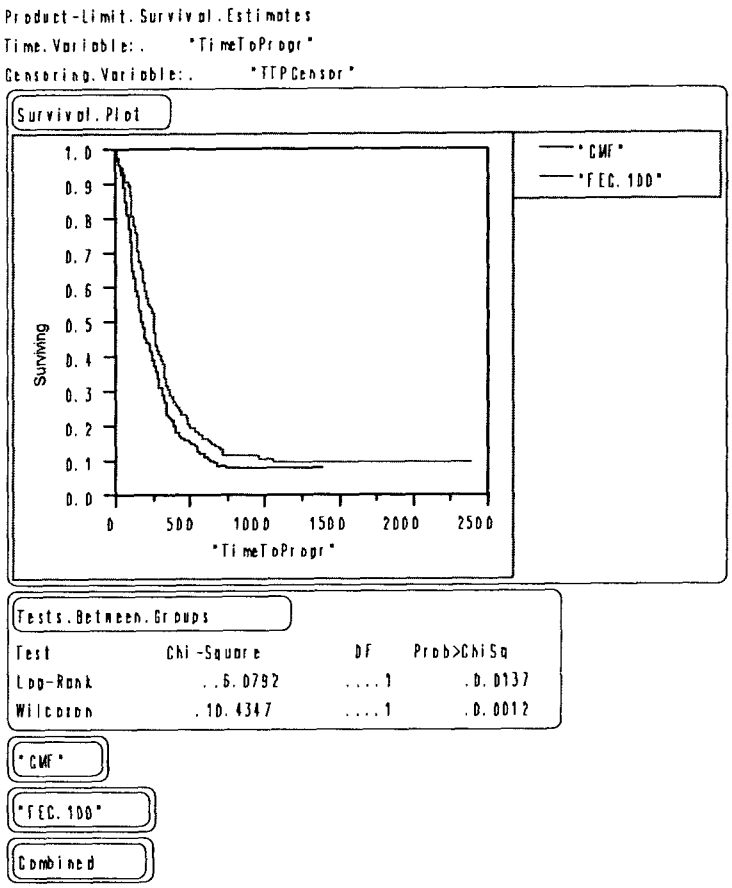
Reviewer Comments:

1. The primary analysis should be performed on all randomized patients. The sponsor's analysis excluded 15% of patients on the trial.

2. The primary analysis should be performed as an unadjusted analysis. Strata are used to balance randomization and are not required as factors in the analysis. Stratified analyses, using the randomization strata, can be used if pre-specified in the protocol. In this protocol, the statistical plan was not fully outlined. We prefer an unadjusted analysis of all randomized patients; the analyses submitted by the sponsor can be considered as secondary supportive analyses.

3. The reviewer analyzed time to progression in all randomized patients, using the TTP dates determined by the sponsor:

Figure 5. Time to progression (sponsor's dates), all randomized patients (n=461)



The median TTP on CMF was 181 days, and the median TTP on FEC was 260 days (p=0.01 by logrank; p=0.001 by Wilcoxon). The difference in TTP between treatment arms was 2.6 months (11 weeks). The ODAC members will be asked to discuss the clinical meaning of this difference in the context of the toxicity data.

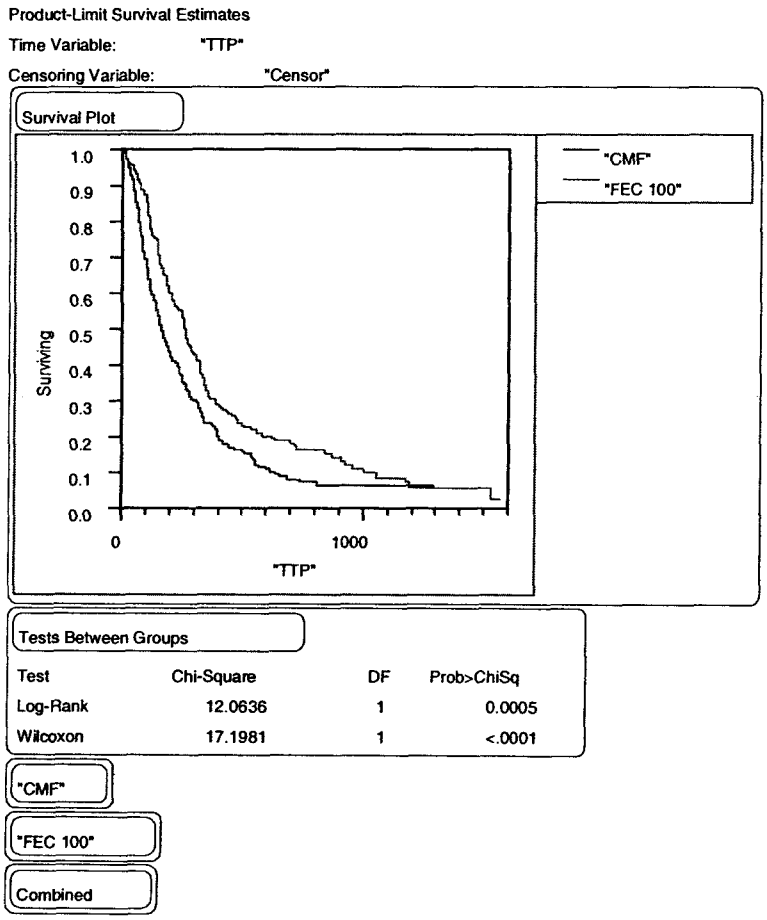
4. The reviewer used the electronic data to independently calculate TTP on each treatment arm. The algorithm requires all lesions to be assessed at each visit, calculates the area of the lesions, compares measurements between all visits in all possible combinations, and selects visits after baseline where the ratio of areas is greater than or equal to 1.25 (25% increase in tumor area). Some patients had non-measurable disease only; some patients had measurable and non-measurable disease. After calculating progression based on measurable lesions, the reviewer created a table of progression, as reported by the investigator, in non-measurable lesions with the date of assessment. The earliest recorded progression date (measurable or non-measurable site) was used. Patients without progression were censored at the last assessment.

This process differs somewhat from the sponsor's method. Patients who received less than 6 cycles and were removed for refusal, toxicity/adverse event, or loss to follow-up were censored at the date of the last clinical or laboratory evaluation of the last visit. If the patient received 6 or more cycles of treatment, they were censored at the last date at

which the patient status was assessed, unless they received chemotherapy or radiotherapy in the absence of progression. In that case, they were censored at the start date of the new therapy (7 on each arm). Despite removal from study, many of these patients had sequential tumor measurements recorded in the CRF and in the database, allowing calculation of the actual time to progression on all patients, rather than calculation of time to progression/time to severe toxicity. Censoring for toxicity might be more appropriately considered in time to treatment failure.

The following curve was generated:

Figure 6. FDA analysis of TTP, 25% increase in the area of any lesion



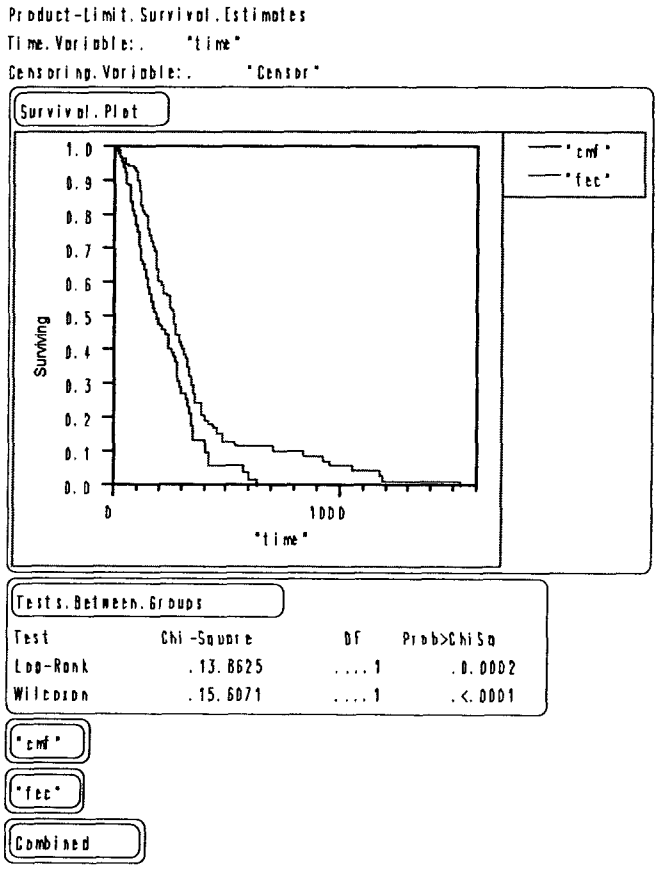
The median time to progression was 168 days on CMF (the sponsor reported 190 days) and 265 days on FEC (the sponsor reported 266 days). The p-values are shown below the graph and were highly significant.

These results are almost identical to those reported by the sponsor and are statistically significant. It is unlikely that censoring for toxicity occurred in a biased manner.

5. Grant Williams, Team Leader, repeated the analysis of TTP but changed the algorithm to measure progression based on a 25% increase in the sum of the areas of all

lesions. The algorithm used in (4) based progression on a 25% increase in the area of any single lesion. The following results were obtained:

Figure 7. TTP, FDA analysis, 25% increase in the sum of the areas of all lesions



In this analysis, median TTP on CMF was 190 days and on FEC was 266 days, identical to the sponsor's results.

11.12.2 Time to treatment failure

Time to treatment failure was analyzed on all patients with a diagnosis of breast cancer, which included 223 patients on FEC and 231 patients on CMF according to the study report. The Kaplan-Meier (KM) curve used 220 and 231 patients respectively and analyzed 205 and 220 events in the respective treatment arms. Median TTF was 187 days on FEC and 147 days on CMF, with a stratified logrank p-value of 0.0080.

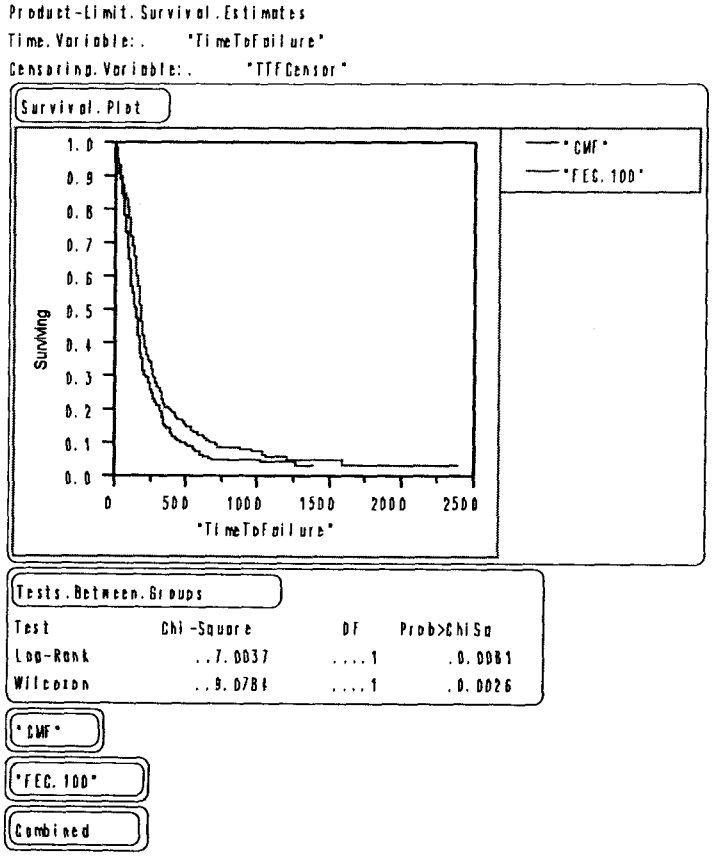
Median TTF as reported in the study report was 6.2 months on FEC and 4.9 months on CMF. The hazard ratio of FEC: CMF was 0.77 (95% CI 0.6, 0.9).

An addendum report to the study (volume 2.33, Appendix 8) calculated TTF in all randomized patients. The patient treated prior to randomization was excluded. The median TTF was 6.2 months for FEC and 5 months for CMF. The stratified logrank test gave a p-value of 0.01.

Reviewer Comments:

1. TTF was not listed in the protocol as an endpoint (primary or secondary).
2. Unadjusted analyses are preferred.
3, The reviewer calculated TTF for all randomized patients in an unadjusted analysis, using the sponsor's dates for time to treatment failure.

Figure 8. TTF in all randomized patients (unadjusted analysis)



The median TTF for CMF was 147 days (4.8 months) and 187 days (6.2 months) for FEC.

3. There was a 1.5 month difference in TTF between the two treatment arms, which was statistically significant in favor of FEC. Whether a 6 week difference in TTF represents clinical benefit will be evaluated in concert with the toxicity data and discussed with the Advisory Committee.

11.12.3 Response rate

Evaluation of response rate was performed in all patients with a diagnosis of breast cancer (223 and 231) and in fully eligible, evaluable, and treated as randomized patients (189 on FEC and 200 on CMF.

The following table summarizes the observed response rates:

Table 66. Best response in all randomized patients with breast cancer (Modified from sponsor's table 24, volume 2.33, page 94)

Response	FEC (n=223)	CMF (n=231)
CR	30 (14 %)	25 (11%)
PR	98 (44%)	81 (35%)
CR + PR	128 (57%)	106 (46%)
NC	42 (19%)	46 (20%)
PD	23 (10%)	54 (23%)
NE	30 (13.5%)	25 (11%)

The difference in CR rate was not statistically significantly different between treatment arms (p=0.4; odds ratio 1.3 with 95% CI 0.7, 2.2). The CR + PR rate was significantly better on FEC than on CMF, with a p-value of 0.01 and an odds ratio of 1.6 (95% CI 1.1, 2.3).

A secondary analysis of eligible and evaluable patients treated as randomized was performed. The overall response rate was 66% for FEC and 52% for CMF (p=0.005), with an odds ratio of 1.8 (95% CI = 1.2, 2.7).

Additional analyses examined response by the number of sites involved and by the presence or absence of visceral involvement. These results are summarized below:

Table 67. Best response (CR + PR) in all randomized patients with breast cancer, analyses by strata (Modified from sponsor's tables 30-37, volume 2.33, pages 100-107).

Strata	FEC (n=221)	CMF (n=231)
Number of sites:		
1-2	86 (58%)	76 (51%)
>2	42 (58%)	30 (37%)
Location:		
Visceral	63 (50%)	58 (43%)
Non-visceral	65 (69%)	48 (50%)

The response rate in patients with more than 2 lesions was significantly better with FEC (p=0.01 for all randomized patients with breast cancer; p=0.006 in evaluable patients). Patients with non-visceral disease had a significantly better response with FEC than with CMF (p=0.007 in randomized breast cancer patients; p=0.005 in evaluable patients).

Duration of response was 8.8 months on FEC and 7.2 months on CMF (logrank test p=0.07).

Reviewer Comments:

1. Analyses should be performed on the entire randomized population in an intent-to-treat basis to avoid bias. It is acceptable to exclude patients who were never treated. The sponsor's analyses by number of sites and location of disease are exploratory in nature. Although randomization was stratified by these factors, the strata were not powered to detect a difference between treatment arms.

2. It is difficult to measure response rate in patients with evaluable non-measurable lesions.

3. The number of patients listed in the summary table for the KM response curve was 128 on FEC and 106 on CMF, with a median duration of response of 263 days and 217 days respectively.

4. The overall response rate was higher on FEC than on CMF. The analyses by strata and by evaluable patients show trends consistent with the finding in the unadjusted analysis.

5. The reviewer did not recalculate response rates, as survival and TTP data were available.

11.12.4 Survival

Overall survival was analyzed for the entire randomized population according to the study report. The Kaplan-Meier curve shows patient totals of 221 and 237 for FEC and CMF respectively. The median survival was 603 days on FEC and 547 days on CMF. The stratified logrank test gave a p-value of 0.24.

Median survivals were reported in the study report as 20.1 months and 18.2 months respectively. The hazard ratio of FEC: CMF was 0.87 (95% CI 0.7, 1.1).

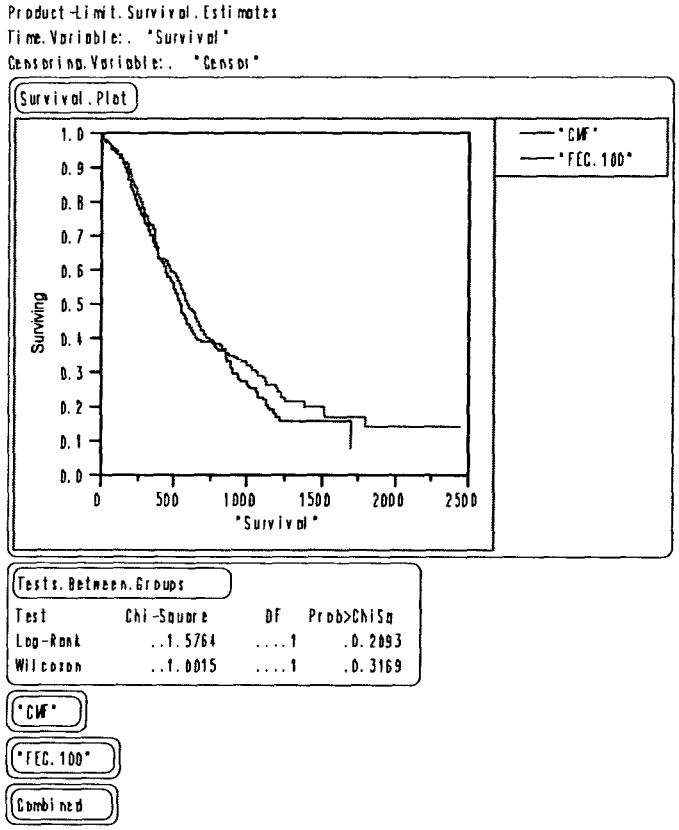
Reviewer Comments:

1. Date of death was audited by the FDA's DSI in the field.

2. From a database query, 161 patients on CMF and 149 patients on FEC had died at the time of the data lock date.

3. The electronic data was re-analyzed by the reviewer to obtain unstratified survival time on the entire randomized population.

Figure 9. Unadjusted overall survival



These results replicate those reported by the sponsor.

11.13 Safety

The safety analysis was performed on all randomized patients who received at least 1 cycle of chemotherapy. Six patients were never treated (5 on FEC and 1 on CMF); 2 patients randomized to CMF received FEC. The number of patients analyzed on FEC is 220 and on CMF is 234.

11.13.1 Mortality, other serious adverse events, and discontinuations due to serious adverse events

11.13.1.a Mortality

Nineteen patients died on study: 10 patients treated with FEC (1 who was randomized to CMF), 8 patients treated with CMF, and 1 patient randomized to FEC who died of progressive disease before she was treated (not included below).

The cause of death is listed below:

Table 68. Cause of death on study

Cause of death	FEC (n=10)	CMF (n=8)
Progressive disease	2	3
Febrile neutropenia	3	2
Pulmonary embolism	3	1
Respiratory failure	1	0
Cerebral infarction	1	0
Pulmonary edema	0	1
Peritoneal hemorrhage	0	1

Reviewer Comments:

1. The narratives for deaths on study were reviewed. On the CMF arm, the peritoneal hemorrhage was unrelated to thrombocytopenia or neutropenia.

2. On the FEC arm, the sponsor lists 3 cases of death from febrile neutropenia and 3 from PE. The narratives suggest that deaths occurred from 2 cases of febrile neutropenia and 4 cases of PE. The case of respiratory insufficiency developed suddenly and resulted in the death of a patient 8 days after C6 of FEC. While it is appropriate to list it as "respiratory insufficiency", this case may also represent pulmonary embolus. Note that there was an additional, non-fatal case of PE reported on the FEC arm (see section 11.13.1.b).

3. If all cases of fatal, non-fatal, and suspected PE are counted, there are potentially 6 cases on FEC, or 2.7% of the randomized arm. This figure is consistent with the incidence of thromboembolic events reported in other cytotoxic breast cancer treatment trials (1-5%).

11.13.1.b Other serious adverse events

Twelve patients on FEC and 9 on CMF withdrew because of non-cardiac serious adverse events. The reasons for withdrawal are summarized below:

Table 69. Reasons for withdrawal from study

Adverse Event	FEC (n=12)	CMF (n=9)
Hematologic toxicity	7	6
Liver toxicity	1	1
Pulmonary emboli	1	0
Thrombophlebitis	1	0
Acute gastroenteritis	1	0
Acute glaucoma	1	0
Toxic dermatitis	0	1
Renal insufficiency, mucositis	0	1

Reviewer Comments:

1. The narratives for these patients were reviewed. The patient on FEC with "acute gastroenteritis" also had bronchitis, mucositis, fever, and pneumonia; her adverse events might be better classified as infectious/hematologic toxicity. The patient with thrombophlebitis also had an extravasation with ulceration and peripheral vein

obliteration, making further treatment mechanically impossible according to the investigator.

2. On the CMF arm, two patients who were removed from study for hematologic toxicity also had grade 3 mucositis. One had grade 3 diarrhea as well. The patient with toxic dermatitis developed cutaneous hypersensitivity after the first cycle of CMF, which recurred on rechallenge with reduced doses.

3. The database was evaluated for serious adverse events. Three patients on CMF experienced phlebitis. Two patients on FEC had deep vein thromboses. No unreported adverse events were detected.

4. Pain on injection and extravasation were reported in the database as present or absent. Ten patients on FEC (5%) and 2 on CMF (1%) experienced extravasation. Three patients on FEC developed complications of the extravasation. One patient developed thrombophlebitis, as noted above. One required antibiotic therapy, and one developed necrosis.

3. A similar percentage of patients in each arm went off study for non-cardiac serious adverse events. The reasons for withdrawal were similar between arms.

11.13.1.c Cardiac toxicity

The protocol indicated that all patients should have an LVEF measured at baseline and at the end of treatment. Patients on FEC were to undergo repeat evaluations at a cumulative dose of 400-500 mg/m^2, at a cumulative dose of 700-800 mg/m^2, and then at each cycle.

The following table summarizes the actual evaluations performed:

Table 70. LVEF determinations on study (Sponsor's table 57, volume 2.33, page 127)

Time of Assessment	Method of Assessment	FEC (n=220)	CMF (n=233)
Baseline only	ECHO	20	78
	MUGA	39	79
Baseline + at least 1 cycles	ECHO	92	56
	MUGA-ECHO	4	4
	MUGA	64	16
No baseline	ECHO	1	0

Of the 460 patients randomized on study, 453 had at least 1 measurement of LVEF at any time (98%). Fifty-nine patients on FEC (26% of the randomized arm) had a baseline evaluation only and cannot be assessed for changes in cardiac function. One hundred fifty-seven patients on CMF (66% of the randomized arm) were evaluated only at baseline. Four patients on each arm did not have the same technique used to evaluate cardiac function. The sponsor excluded these patients and analyzed 228 patients, 156 on FEC (70% of the treatment arm) and 72 on CMF (30%), for changes in cardiac function.

On the FEC arm, 59% of patients were evaluated with ECHO and 41% were evaluated with MUGA. On the CMF arm, the percentages were 78% and 22% respectively. Changes were calculated as the difference between the baseline and each subsequent measurement. A significant change was defined as $\geq$ 20% decrease below the baseline value and/or $\geq$ 10% absolute decrease below the lower limit of normal for the institution.

The following table summarizes changes in cardiac function according to dose received:

Table 71. Cardiac function in patients evaluable for LVEF (Sponsor's table 58, volume 2.33, page 128)

Dose administered (mg/m^2)	FEC				CMF			
	Cumulative number of patients	Cumulative no. pts. with prior mediastinal RT	≥ 10% below normal	≥ 20%	Cumulative number of patients	Cumulative no. pts. with prior mediastinal RT	≥ 10% below normal	≥ 20%
1--100	156				72	1		
100--≤ 200	154	3			72			
200--≤ 300	154	3			64			
300--≤ 400	150	7	2	3	57	1		
400--≤ 500	134	6		3	51	2		1
500--≤ 600	117	4		1	36	1		
600--≤ 700	87	5	1	4	32	1		
700--≤ 800	61	2		1	13			
800--≤ 900	46	3		3	0			
900--≤ 1000	14	1		2	0			

On FEC, 19 of 156 evaluable patients presented with significant changes in cardiac function (12%); 1 patient had 2 episodes. One of 72 evaluable patients on CMF (1%) had significant cardiac changes. Events on FEC were not observed below 300 mg/m^2 and were observed with increased frequency as cumulative dose increased.

Ten patients on FEC were taken off study for changes in LVEF. One patient was removed for progressive disease, but she also had a 33% drop in LVEF. Three patients were removed for ECG changes, and 2 for the development of congestive heart failure (CHF). Two additional patients developed CHF, although CHF was not listed by the investigator as the reason for treatment withdrawal.

Reviewer Comment:

1. Thirty percent of patients on FEC received less than 400 mg/m^2 cumulative dose of epirubicin. It is likely that failure to obtain a second cardiac evaluation was related to progressive disease.

2. The low number of patients on CMF who had repeat evaluations was probably due to the unblinded nature of the study and the lack of reported cardiac toxicity with CMF.

3. The number of patients evaluated with both MUGA and ECHO at different time points is small. It is appropriate to exclude these patients from analysis, as the results from these two studies frequently do not correlate.

4. In Table 69, patients with a history of mediastinal irradiation are listed. However, none of the patients with cardiac toxicity had received prior mediastinal irradiation.

5. The narratives for patients who went off study for cardiac toxicity were reviewed. Information from these patients is summarized in the following table.

Table 72. Summary of cardiac toxicity on HEPI 013

Treatment	Patient ID	Age	Event	Symptoms	Cumulative epirubicin (mg/m^2)	Time to event
FEC	1-30	47	62% to 36%; increased to 43% 2 yrs later	No	354	C4
	5-27	62	LVH on ECG; LVEF 50%	Yes; SOB, tachycardia	460	C5
	5-31	47	71% to 44%	No	750	C7
	5-45	56	57% to 40%	No	397	C4
	7-17	63	58% to 48%; 48% to 44%	No	371 575	C4 C7
	12-57	61	66% to 48%; improved to baseline on F/u	No	610	C6
	16-16	47	77% to 50%; dilation of LV	No	488	C8
	17-3	21	LVEF 28%	Yes; classic CHF	900	C9
	17-12	51	50% to 35%	Yes, mild CHF	700	C7
	21-13	63	70% to 54%	Yes	600	C6
	29-75	69	Tachyarrhythmia; required cardiac medication	Yes	244	C3
	48-6	62	ECG w/ ischemia; ECHO showed normal LVEF but anterolateral hypokinesis	No	342	C5
	51-7	54	78% to 54%; improved to 60% with f/u	No	620	C6
	57-19	65	Clinical CHF after C1D1; resolved with medical therapy	Yes	50	C1
	58-35	49	Normal LVEF but apical hypokinesis. LVEF dropped to 23% 6 mo later	No, then symptomatic 6 mo later	700	C7
	59-56	65	63% to 48%; LVH with dysfunction	No	900	
	59-67	63	68% to 62%; diastolic dysfunction	DOE, peripheral edema	398	C4
	48-4	61	Enzymes c/w MI. Received all additional cycles without problems	Chest pain, dyspnea, confusion	100	C1
CMF	56-23	69	Decreased LVEF with abnormal wall motion	No		C7
	65-3	66	86% to 53%	Unknown		C6

Abbreviations: LVH = left ventricular hypertrophy; SOB = shortness of breath; LV = left ventricle; MI = myocardial infarction; DOE = dyspnea on exertion

6. The electronic database was queried to obtain an independent list of patients who were removed for cardiac toxicity. The parameters were set at a decrease of 20

percentage points in the LVEF compared to baseline, and any value below 40. The institutional lower limits of normal for LVEF were not given; 50 was arbitrarily chosen as the lower limit, and 40 represents an approximation of a drop of 10 percentage points to below normal. Additional patients, other than those in the above table, were identified:

Table 73. Patients with ≥ 20% decrease in LVEF or follow-up LVEF value ≤ 40%

Treatment arm	Patient ID	LVEF values	Time of event
FEC	13-5	70 to 47	Follow-up 17
	18-2	87 to 54	C6
	21-16	90 to 50	C9
	30-45	91 to 43 to 38	C9 Follow-up 4
	30-62	66 to 36	C9
	34-8	70 to 47	Follow-up 3
	34-9	62 to 42	Follow-up 4
	51-2	80 to 60	C8
	53-8	71 to 47	C4
	55-2	89 to 67	C5
	56-37	72 to 52	C9
	57-4	85 to 61	C9 (stable through follow-up 8)
	57-38	83 to 61	Follow-up 1
	59-32	63 to 41	Follow-up 2
	61-7	76 to 56	C4
	61-15	77 to 57	C9
	61-17	67 to 45	Follow-up 4
	65-2	80 to 54	C7
	70-2	32	Baseline
	70-3	33	Baseline
CMF	57-40	81 to 61	Follow-up 1
	58-51	76 to 52	Follow-up 4
	59-34	60 to 40	Follow-up 3
	61-18	80 to 57	Follow-up 2
	70-1	33	Baseline
	70-4	32	Baseline
	70-5	35	Baseline

Eight additional patients on FEC experienced falls in LVEF values to below 50, a level that might be associated with subsequent functional impairment.

7. Review of the line listings for cardiac toxicity (volume 2.37, listing 8.2) and the electronic database showed symptoms in 2 patients on CMF and 8 patients on FEC that could be consistent with cardiac dysfunction. These patients are not included in the above tables.

The sponsor was asked to discuss these patients and supplied narratives for them. The patients and their courses are summarized below:

FEC:

Patient 5-62 AR: Paroxysmal nocturnal dyspnea and tachycardia; occurred after treatment was discontinued.

Narrative: The patient had an LVEF of 48% when these symptoms occurred, after 5 cycles of chemotherapy. The LVEF increased to 52% 5 days later. She went off-study at this time because of progressive disease. Subsequent LVEFs were reported as normal, but no values were given.

Patient 11-29 IT: Tachycardia, dyspnea after C1

Narrative: Documented Candida pneumonia

Patient 13-1 GR: Angina after C3

Narrative: PACs at baseline. This patient developed angina, SVT after cycle 4 and went off-study because of disease progresssion. The LVEF was 53% (baseline 60%) and decreased to 47% one week later. No other LVEF assessments were made.

Patient 24-82 IT: DOE after C2

Narrative: Normal LVEF of 65% and normal ECG; symptoms resolved.

Patient 26-13 DD: DOE and tachycardia at C3

Narrative: Symptoms present at baseline; patient had hypertension and pulmonary metastases

Patient 34-13 URSS: Peripheral edema, tachycardia at C5

Narrative: The patient had type I AV block at study entry. At cycle 5, she developed the above symptoms and was found to have an LVEF of 55% (67% at baseline), with ST-T wave changes and abnormal repolarization on ECG. She went off study for disease progression, died 3 months later of PD, and had no further cardiac evaluations.

Patient 52-3 CS: Shortness of breath, DOE, edema, and tachycardia after C4.

Narrative: The symptoms resolved spontaneously within 2 days. LVEF was 53% (67% at baseline); ECG showed left anterior hemiblock. At cycle 6, the LVEF was 50%. At 4 months of follow-up, the LVEF was 55%.

Patient 56-21 PL: SOB, DOE, cough, tachycardia after C4

Narrative: The patient had pulmonary metastases and symptoms at baseline. The LVEF at cycle 5 was 54%, decreased from 70% at baseline. She was included in the sponsor's tabulation of significant LVEF changes.

CMF:

Patient 26-2: DOE, nocturia, tachycardia after C1

Narrative: The patient had angina and valvular insufficiency at baseline. No changes in ECG or LVEF at cycle 3.

Patient 49-11: Peripheral edema

Narrative: The patient required diuretics for treatment of peripheral edema. The LVEF was 59%, compared to 67% at baseline.

Four patients on FEC (5-62, 13-1, 34-13, and 52-3) may have had exacerbation of cardiac problems by epirubicin administration, but it is difficult to directly attribute symptoms to study drug.

8. Queries of the electronic database showed 4 additional patients with CHF on FEC. These patients are not included in Tables 70 or 71, and narratives were not supplied. These patients are 5-29, 13-5, 23-11, and 58-24. Patient 13-5 appears in the reviewer's table of changes in LVEF. The sponsor provided narratives for these patients.

AR 5-29: This 38 year old woman had a history of hepatitis A and Berger's disease and was taken off study after 1 cycle of therapy due to liver toxicity. One month later, she began therapy with doxorubicin 50 mg/m^2, vinorelbine, and 5-FU. Just prior to cycle 2, she developed dyspnea and a drop in the LVEF from 54% at baseline to 46%. In subsequent visits, no signs or symptoms of CHF were reported.

Reviewer's assessment: Cannot rule out an effect of epirubicin 100 mg/m^2 plus doxorubicin 50 mg/m^2 on cardiac function, although cardiac dysfunction is rare at these cumulative doses.

GR 13-5: This 65 year old woman received 9 cycles of FEC. Approximately 1.5 years later, she progressed and received radiotherapy to the right breast and tamoxifen. Two years later, she developed dyspnea and was found to have LBBB on ECG and an LVEF of 47%. She was then treated with taxotere and navelbine, with continued dyspnea until 3/17/97. Symptoms resolved by 11/11/97.

Reviewer's assessment: Drop in LVEF and dyspnea are likely to be related to a cumulative epirubicin dose of approximately 900 mg/m^2 and no intervening chemotherapy.

UR 23-11: This 62 year old women received FEC for 9 cycles. She was reported to have CHF at cycle 4, although the symptom checklist for cardiovascular disease was negative. A chest X-ray, ECG, and LVEF were not performed. Subsequent X-rays and cardiac assessments were normal.

Reviewer's assessment: Probably an incorrect report of CHF

SL 58-24: This 54 year old woman received 3 cycles of FEC and was taken off study due to progressive disease. She received tamoxifen, then aminoglutethimide. Eight months after discontinuing epirubicin, she developed dyspnea on exertion. The ECG showed "myocardial hypoxia" with an LVEF of 58%. Ten months after this event she developed ischemic cardiomyopathy according to the treating physician.

Reviewer's assessment: Events may be related to epirubicin cumulative dose of 300 mg/m^2, although cardiac dysfunction is uncommon at this dose.

9. Of note is the fact that 5 of 5 patients entered at site 70 had baseline LVEF values between 30 and 35. The sponsor was asked about this finding. At that site, a normal LVEF at rest by ECHO was defined as 30-40%.

10. Few patients (7 on CMF and 17 on FEC) entered the trial with a history of cardiac problems. The majority of these problems were related to nonspecific rhythm disturbances. The occurrence of cardiac toxicity did not correlate with baseline cardiac history.

11. A total of 29 patients (19 with drops in EF, 8 patients from the reviewer's query with LVEF below 50, and the 2 additional CHF patients listed in point 8)

experienced cardiac toxicity. This number represents 13% of the patients randomized to FEC.

11.13.2 Laboratory abnormalities

11.13.2.a Hematology

Baseline laboratory values were normal in greater than 91% of patients at baseline. Reported abnormalities included grade 1-2 toxicities; the most common was a 9% incidence of grade 1 anemia at entry on both arms.

Patients were evaluable for safety analysis if at least one WBC, neutrophil, and platelet count was obtained between days 8-15 and for hemoglobin if at least one count was obtained during the cycle. The sponsor documented the number of patients evaluable for each analysis; over 99% of patients were evaluable for all hematologic endpoints. Analyses were performed for all randomized patients in order to capture severe toxicity that may have led to early drop-out. Hematologic toxicity is summarized in the following table:

Table 74. Hematologic toxicity: Worst WHO grade in randomized treated patients (Sponsor's table 42, volume 2.33, page 112

Parameter	FEC (n=220)	CMF (n=234)
WBC:		
No data	0	1 (0.4%)
Grade 0-2	75 (34%)	98 (42%)
Grade 3	85 (39%)	100 (43%)
Grade 4	60 (27%)	35 (15%)
Neutrophils:		
No data	2 (1%)	3 (1%)
Grade 0-2	47 (21%)	75 (32%)
Grade 3	77 (35%)	80 (34%)
Grade 4	94 (43%)	76 (33%)
Platelets:		
No data	0	1 (0.4%)
Grade 0-2	205 (93%)	219 (94%)
Grade 3	11 (5%)	11 (5%)
Grade 4	4 (2%)	3 (1%)
Hemoglobin:		
Grade 0-2	194 (88%)	212 (91%)
Grade 3	20 (9%)	20 (9%)
Grade 4	6 (3%)	1 (0.4%)

The total number of administered cycles was 1295 on FEC and 1263 on CMF. The worst WHO grade per cycle is summarized in the following table:

Table 75. Hematologic toxicity: Worst WHO grade in all cycles (Sponsor's table 46, volume 2.33, page 116)

Parameter	FEC (n=1295)	CMF (n=1263)
WBC:		
No data	2 (0.2%)	3 (0.2%)
Grade 0-2	785 (61%)	927 (73%)
Grade 3	397 (31%)	287 (23%)
Grade 4	111 (9%)	46 (4%)
Neutrophils:		
No data	19 (2%)	24 (2%)
Grade 0-2	656 (51%)	818 (65%)
Grade 3	393 (30%)	299 (24%)
Grade 4	227 (18%)	122 (10%)
Platelets:		
No data	2 (0.1%)	3 (0.2%)
Grade 0-2	1273 (98%)	1245 (99%)
Grade 3	16 (1%)	12 (1%)
Grade 4	4 (0.3%)	3 (0.2%)
Hemoglobin:		
Grade 0-2	1248 (97%)	1230 (98%)
Grade 3	37 (3%)	26 (2%)
Grade 4	8 (1%)	2 (0.1%)

The sponsor presented data on hematologic toxicity for days 19-24 and days 25-30 of cycles lasting longer than 30 days. Grade 3-4 neutrophil toxicity was observed in 38% of patients on FEC and 26% of patients on CMF for days 19-24. Grade 3-4 neutrophil toxicity was observed in 7% and 9% of patients respectively during days 25-30.

On the FEC arm, 23 patients experienced 29 events of febrile neutropenia. On the CMF arm, 18 patients had 19 episodes of febrile neutropenia.

Thirteen patients received G-CSF as supportive care during the trial.

Reviewer Comments:

1. FEC was associated with more grade 3-4 neutropenia than CMF, when considered by patient or by cycle.

2. Three patients on FEC and 2 on CMF died of febrile neutropenia.

3. In Table 76, there was no reported difference in the incidence of fever, infection, or hemorrhage between treatment arms. The sponsor (volume 2.33, table 54, page 124) reported more cases and episodes of febrile neutropenia on the FEC arm compared to CMF. Overall, it appears that the predominant hematologic toxicity of FEC was neutropenia, with a 10% incidence of febrile neutropenia compared to 8% on CMF.

3. The degree of neutropenia might be ameliorated by the use of colony stimulating factors.

11.13.2.b Other laboratory tests

Few patients had baseline laboratory abnormalities; most of these were limited to grade 1 toxicity.

Abnormalities in non-hematologic laboratory parameters during the trial are summarized below.

Table 76. Worst WHO grade by patient (Sponsor's table 50, volume 2.33, page 120)

Laboratory test	FEC	CMF
Bilirubin:		
Grade 0	204	209
Grade 1	11	18
Grade 2	2	2
Grade 3	0	0
Grade 4	0	1
SGOT:		
Grade 0	156	151
Grade 1	53	62
Grade 2	6	9
Grade 3	1	7
Grade 4	1	1
Creatinine:		
Grade 0	206	222
Grade 1	10	8
Grade 2	0	0
Grade 3	1	0
Grade 4	0	0
BUN/Urea:		
Grade 0	204	219
Grade 1	10	9
Grade 2	2	0
Grade 3	0	1
Grade 4	1	1

Reviewer Comment:

1. Few patients experienced renal or hepatic toxicity during the trial. Two patients on FEC and 9 patients on CMF were found to have grade 3-4 hepatic toxicity. Two patients on each arm experienced grade 3-4 renal toxicity.

11.13.3 Clinical toxicity

The sponsor reported baseline clinical toxicities, which were absent in the majority of patients.

The following table summarizes symptoms that occurred during therapy:

Table 77. Clinical toxicities: Worst WHO grade by patient (Sponsor's table 52, volume 2.33, page 122)

Adverse Event	FEC (n=220)	CMF (n=234)
Nausea and vomiting:		
Grade 0	35 (16%)	42 (18%)
Grade 1	30 (14%)	50 (21%)
Grade 2	109 (50%)	110 (47%)
Grade 3	43 (20%)	32 (14%)
Grade 4	3 (1.4%)	0
Diarrhea:		
Grade 0	181 (82%)	178 (76%)
Grade 1	24 (11%)	31 (13%)
Grade 2	9 (4%)	17 (7%)
Grade 3	3 (1.4%)	4 (2%)
Grade 4	0	0
No data	3 (1.4%)	4 (2%)
Mucositis:		
Grade 0	117 (53%)	130 (56%)
Grade 1	23 (11%)	32 (14%)
Grade 2	50 (23%)	32 (14%)
Grade 3	26 (12%)	29 (12%)
Grade 4	1 (0.5%)	7 (3%)
No data	3 (1.4%)	4 (2%)
Infection:		
Grade 0	144 (66%)	168 (72%)
Grade 1	31 (14%)	22 (9%)
Grade 2	32 (15%)	30 (12%)
Grade 3	9 (4%)	7 (3%)
Grade 4	1 (0.5%)	3 (1%)
No data	3 (1.4%)	4 (2%)
Fever:		
Grade 0	157 (71%)	170 (73%)
Grade 1	29 (13%)	21 (9%)
Grade 2	29 (13%)	37 (16%)
Grade 3	1 (0.5%)	2 (1%)
Grade 4	1 (0.5%)	0
No data	3 (1.4%)	4 (2%)
Hemorrhage:		
Grade 0	208 (95%)	210 (90%)
Grade 1	3 (1.4%)	11 (5%)
Grade 2	4 (2%)	7 (3%)
Grade 3	1 (0.5%)	1 (0.4%)
Grade 4	0	1 (0.4%)
No data	3 (1.4%)	4 (2%)
Alopecia:		
Grade 0	24 (11%)	92 (39%)
Grade 1	7 (3%)	53 (23%)
Grade 2	40 (18%)	53 (23%)
Grade 3	142 (65%)	32 (14%)
Grade 4	4 (2%)	0
No data	3 (1.4%)	4 (2%)

Cutaneous:		
Grade 0	201 (91%)	212 (91%)
Grade 1	10 (5%)	12 (5%)
Grade 2	6 (3%)	5 (2%)
Grade 3	0	1 (0.4%)
Grade 4	0	0
No data	3 (1.4%)	4 (2%)
Neurotoxicity/CNS:		
Grade 0	213 (97%)	224 (96%)
Grade 1	2 (1%)	3 (1%)
Grade 2	1 (0.5%)	0
Grade 3	1 (0.5%)	1 (0.4%)
No data	3 (1.4%)	4 (2%)
Neurotoxicity/Peripheral:		
Grade 0	212 (96%)	226 (97%)
Grade 1	3 (1.4%)	3 (1%)
Grade 2	2 (1%)	0
Grade 3	0	1 (0.4%)
No data	3 (1.4%)	4 (2%)
Pain:		
Grade 0	143 (65%)	142 (61%)
Grade 1	29 (13%)	25 (11%)
Grade 2	34 (16%)	45 (19%)
Grade 3	10 (5%)	18 (8%)
No data	4 (2%)	4 (2%)

The sponsor presented data on the worst WHO grade by cycle; results are similar to those cited above. Other than alopecia, the incidence of these grade 3-4 toxicities was less than 6%.

Reviewer Comments:

1. Few patients had any symptoms at baseline that might be used as additional measures of clinical benefit. Pain was the most common complaint, and it was scored as grade 1-2 in the majority of patients. Only 5% of patients on each arm had grade 3 pain. During therapy, 5% of FEC patients experienced grade 3 pain as the worst grade of toxicity, compared to 8% of CMF patients. There was no significant difference between treatment arms.

2. During treatment, patients on FEC had more grade 3-4 nausea and vomiting (21% versus 14%). According to an MS Access query, 73 patients (33%) on FEC and 62 patients (26%) on CMF used ondansetron during the trial.

3. Alopecia occurred with significantly greater frequency and severity ($p<0.001$ for each parameter) on FEC than on CMF, consistent with clinical use and other published reports.

4. The electronic database was used to verify reported cases of adverse events, hematologic, and chemistry abnormalities. The database queries gave results that were within 1-2 patients of the numbers reported by the sponsor.

11.14 Quality of life

Quality of life data were collected on this study. The sponsor did not provide an analysis of the data, due to the poor compliance in the use of the questionnaire and data insufficiency.

11.15 Differences between the published report and the study report of Trial HEPI 013

The results of the study have been published in abstract form only (ASCO proceedings 1995, volume 14, abstract 156, page 114). This abstract presented interim results. The general conclusions are similar to those presented here, although the reported values for the endpoints differ from those in the final analysis.

11.16 Sponsor's summary of safety and efficacy

The sponsor noted that the FEC arm resulted in a statistically significant improvement in response rate, time to progression, and time to treatment failure. No difference in survival was observed. The dose-intensity of FEC was maintained in this study. The sponsor suggests that survival is related to the number of complete responses that are achieved, and that the number of CRs was similar in both treatment arms.

Overall, FEC was well-tolerated despite its increased myelosuppression and is active in the metastatic setting.

11.17 Reviewer's summary of safety and efficacy

Study HEPI/013 compared FEC with CMF as first-line therapy of metastatic breast cancer patients.

The strengths of the study included:

- A comparator arm that used a relatively dose-intense CMF regimen
- Maximizing the dose of epirubicin at the expense of cyclophosphamide and 5-FU
- Stringent criteria for dose reduction
- Statistically significant difference in TTP in favor of FEC

The weaknesses of the study included:

- No survival difference (trend in favor of FEC)
- Statistical plan developed retrospectively
- Limitation of treatment to 6 cycles with follow-up until progression
- Cardiac evaluation optional after the conclusion of treatment
- Increased cardiac toxicity on FEC
- Increased febrile neutropenia, nausea, vomiting on FEC [more mucositis and diarrhea on CMF]
- Poor compliance with quality of life evaluations

The FEC regimen resulted in a statistically significant improvement in TTP in breast cancer patients with no prior chemotherapy for metastatic disease. The absolute difference in TTP between the FEC and CMF arms was 2.5 months. No survival advantage was observed. Whether these findings constitute evidence of efficacy will be discussed in a session of the June ODAC meeting.

Time to progression may offer clinical benefit to patients, provided that the toxicity of the regimen is acceptable and that the length of time before disease worsens is clinically meaningful. In this trial, treatment with FEC improved TTP over a dose-intense CMF comparator by 2.5 months, just at the limit considered to be clinically meaningful by our ODAC consultants. The acute toxicities of FEC included myelosuppression, febrile neutropenia, nausea, and vomiting. The chronic toxicity was predominantly cardiotoxicity, manifested by drop in LVEF and/or clinical signs of congestive heart failure. The acute toxicities, while significantly different from those on CMF, did not result in a high drop-out rate or a high patient refusal rate, suggesting that patients were able to continue therapy. The severity and incidence of these toxicities might be expected to drop with use of prophylactic serotonin-specific antiemetic therapy, colony stimulating factors, and/or prophylactic antibiotics. The cardiac toxicity does not appear to be greater than that associated with doxorubicin. While it cannot be prevented entirely, selection of patients with normal baseline cardiac function and careful monitoring of cardiac status as clinically indicated may help to decrease the number of clinically evident cases of CHF.

In this study, a survival difference between FEC and CMF was not observed. A dose-intense CMF regimen was used, resulting in a comparator arm with greater activity than that generally reported in the literature for CMF. Patients have been followed for approximately 5 years; 67% of the patients on each arm have died. It is possible that further follow-up might show a divergence of the curves, although one might expect a trend favoring one arm to have emerged at this analysis point. Another possibility is that subsequent cross-over to an anthracycline might obscure a survival benefit. The database was queried about subsequent therapy, and the following results were obtained.

Table 77a. Subsequent anthracycline use, study HEPI/013

Anthracycline	FEC 100 (n=223)	CMF (n=237)
Epirubicin	16	44
Doxorubicin	5	41
Mitoxantrone	19	20
Total	40 (18%)	105 (44%)

Almost half the patients on CMF subsequently received an anthracycline-based chemotherapy regimen, which may have prolonged survival in the control group.

Overall, FEC appears to have clinically meaningful activity and manageable toxicity. The adjuvant data, which show a significant advantage in relapse-free survival for FEC over CMF, are supportive of these data. The adjuvant survival data show an advantage for FEC 100 over FEC 50, and a trend towards improved survival with CEF compared to CMF, also supportive. The results of this trial support approval for the first-line therapy of metastatic breast cancer, if TTP is considered an acceptable endpoint for efficacy.

12.0 Advanced Breast Cancer: Study HEPI 010

Title: Multinational international randomised phase III study comparing high dose to conventional dose epirubicin in combination with cyclophosphamide and 5-fluorouracil as primary therapy in advanced breast cancer patients.

Trial Accrual Dates:	**July 1989 to February 1992**
Data Lock Date:	**April 15, 1996**
Sites:	**43 centers (38 active) in 10 non-U.S. countries**

12.1 Rationale and objectives

12.1.1 Rationale

Preclinical and clinical evidence suggested that epirubicin might demonstrate a dose-response curve, with greater anticipated benefit with higher doses compared to standard doses. A new set of phase I trials and additional clinical investigations in non-breast cancer malignancies indicated that higher doses were well-tolerated. Epirubicin, in preliminary studies, was shown to have a more favorable side effect profile than doxorubicin, with less myelosuppression and a higher dose threshold for cardiac toxicity. This prospective randomized trial was designed to evaluate whether increased epirubicin dose resulted in an improved outcome in the first-line treatment of metastatic breast cancer.

12.1.2 Objectives

- To determine whether high-dose epirubicin produces a significant prolongation of median survival of patients with metastatic breast cancer who have not received chemotherapy for this stage of disease
- To determine whether high dose epirubicin can significantly increase the response rate (CR + PR) in this patient population compared to standard dose
- To compare the time to best response
- To compare response duration and time to progression of both treatment groups
- To compare the acute toxicities and cardiac toxicity of both regimens
- To compare the quality of life of patients receiving high dose epirubicin to those receiving standard dose

Reviewer Comments:

1. Survival was the prospectively defined primary endpoint.

2. Response rate was the secondary objective. For regulatory purposes, response rate is used for accelerated approval. In this application for full approval in first-line therapy of metastatic breast cancer, survival and time to progression analyses take precedence.

12.2 Design

12.2.1 Dose and schedule

This trial was a multicenter open-label randomized phase III trial of FEC 100 versus FEC 50. The regimens were as follows:

ARM A:	5-FU	500 mg/m^2 IV D1
	Epirubicin	100 mg/m^2 IV D1
	Cyclophosphamide	500 mg/m^2 IV D1
ARM B:	5-FU	500 mg/m^2 IV D1
	Epirubicin	50 mg/m^2 IV D1
	Cyclophosphamide	500 mg/m^2 IV D1

Cycles were repeated every 3 weeks. Arm A was planned to allow dose escalations of epirubicin to produce granulocyte nadirs of 500-<1000 (after the protocol amendment) and/or platelet nadirs of 40,000-<70,000 and/or mucositis $\leq$ grade 2. Escalation was not permitted on Arm B, but dose modifications were permitted to address toxicity.

Ideal body weight, rather than actual body weight, was used to calculate BSA. Weights were measured prior to each cycle. BSA was recalculated for a significant change in the weight (not defined).

Patients were scheduled to receive a minimum of 3 cycles of chemotherapy unless there was clear evidence of progression. Patients who achieved a CR were to receive at least 6 cycles. If the CR occurred at C6, they were to receive an additional 2 cycles of treatment. Patients with stable disease or a PR after C6 were to stop therapy.

Reviewer Comments:

1. Dose escalation on Arm A permitted a true test of dosing to maximum tolerated levels on an individual basis.

2. In the absence of progression, patients were scheduled to receive 6-8 cycles of therapy and then undergo observation. The design is acceptable, although not consistent with common practice in the United States. One concern raised by the study design is the comparability of follow-up on the two arms, and the incidence of additional therapy in the absence of progression.

12.2.2 Dose modifications

12.2.2.a Hematologic toxicity

On Arm A, escalation was permitted to achieve adequate nadir counts. Escalation levels were defined as follows:

Table 78. Epirubicin escalation levels, Arm A (modified from sponsor's text, volume 2.44, page 185)

Description	Level	Dose
Escalation	+2	120 mg/m^2
Escalation	+1	110 mg/m^2
Starting dose	0	100 mg/m^2
De-escalation	-1	90 mg/m^2
De-escalation	-2	80 mg/m^2

Doses on Arm A were to be modified for D1 counts. Further de-escalation below 80 mg/m^2 was not permitted on Arm A. Interim blood counts were required for at least the first 4 cycles, between days 10 and 14 to determine the nadir count. Nadir counts were also used to modify doses. These changes are summarized in the following table.

Table 79. Epirubicin dose modifications, Arm A (adapted from sponsor's text, volume 2.44, pages 185-6)

Parameter	Counts	Dose modification
Pretreatment (D20-21) counts/events	WBC ≥ 4000 ***and*** platelets ≥ 100,000	Treat on D21; adjust dose according to nadir counts
	WBC < 4000 ***and/or*** platelets < 100,000	Hold therapy. Repeat CBC weekly until normal, then adjust doses based on nadir counts. If no recovery after 2 weeks, off study
	Mucositis grade 3-4	Delay until grade 0
Nadir (D10-14) counts/events	Neutrophils ≥ 1000 ***and*** platelets ≥ 70,000 ***and*** GI mucositis ≤ 1	Increase one dose level
	Neutrophils ≥ 500 and <1000 ***and/or*** Platelets ≥ 40k and < 70k ***and/or*** GI mucositis ≤ 2	Same dose
	Neutrophils < 500 ***or*** platelets < 40,000 ***or*** Mucositis grade 3	Decrease one dose level. May use prophylactic sucralfate and PGA2 prior to dose reduction for first episode of mucositis 3 alone
	Mucositis grade 4	Decrease two dose levels. May use prophylactic sucralfate and PGA2 prior to dose reduction
Febrile neutropenia		Decrease 2 dose levels. May re-escalate by 1 dose level if nadirs show granulocytes ≥ 1000 and platelets ≥ 70,000

On Arm B, dose escalations were not permitted. Dose reductions were as follows:

Table 80. Dose reductions on Arm B

Parameter	Counts	Dose modification
Pretreatment counts (D20-21)	WBC $\geq$ 4000 *and* platelets $\geq$ 100,000	Full doses of all 3 drugs
	WBC < 4000 *and/or* platelets < 100,000	Hold therapy. Repeat CBC weekly. If no recovery after 2 weeks, off study
Mucositis	Grade 3-4	Prophylaxis with sucralfate and PGA2
	Second episode grade 3-4	Reduce all 3 drugs by 25%

12.2.2.b Non-hematologic toxicity

On Arm A, epirubicin was reduced one dose level for any grade 3 and two dose levels for any grade 4 toxicity except alopecia, nausea, and vomiting. Metoclopramide and dexamethasone were recommended for treatment of grade 3-4 vomiting on the high dose arm. If grade 3-4 vomiting persisted after this treatment, epirubicin was to be decreased by one dose level for grade 3 toxicity and 2 dose levels for grade 4 toxicity. Any further need for dose decreases (i.e., dose below 80 mg/m^2) was an off-study criteria. Ice caps were permitted.

On Arm A and B, the following dose adjustments were made for liver function abnormalities:

Table 81. Epirubicin dose adjustments for liver function tests (sponsor's schematic, volume 2.44, page 189)*

Bilirubin		SGOT	% of planned epirubicin dose
$\leq$ 2	***AND***	< 3X normal	100%
2-3	***OR***	3-5X normal	50% *
>3	***OR***	> 5X normal	0%

*In Arm A, dose reduction of epirubicin below 80 mg/m^2 was an off-study criteria

12.2.3 Baseline and follow-up evaluations

The schedule for baseline and follow-up evaluations is included in Appendix I. Cardiac monitoring was required at baseline with either a MUGA or an ECHO and was repeated after a cumulative dose of 350-400 mg/m^2 and before each subsequent course of therapy. The same technique was to be used for each evaluation. A repeat study was performed 2-4 months after stopping therapy, if the patient was taken off-study for CHF or changes in LVEF. ECGs were obtained at the start of treatment, prior to each cycle, and at the off-treatment visit.

Patients were followed every 3 months until death.

Quality of life evaluations were completed before therapy and every 3 weeks. The instrument used was the FLIC, a 22-item inventory in which each item is scored from 1-7 by placing a vertical line through the scale to correspond with the patient's

feelings. The patient is asked to base her answers on the past week, including the day of assessment.

12.3 Randomization and stratification

Patients were centrally randomized in Milan and were stratified by predominant site of disease (predominantly visceral and soft tissue versus predominantly bone), and by number of metastases (1-2 sites versus greater than 2). The amendment of 11/9/89 eliminated the separate randomization process for Austria and added central randomization balanced by center.

Reviewer Comments:

1. A subsequent protocol amendment balanced by center.
2. The stratification factors balance for the most important predictive factors for response to chemotherapy. The inclusion criteria defined acceptable performance status and disease-free interval.

12.4 Protocol amendments

The protocol was amended on November 9, 1989 and on September 14, 1990.

November 9, 1989:

- Changed escalation of epirubicin on Arm A to produce neutrophil nadirs of 500-1000 instead of 300-1000.
- Included patients with locoregional metastases after mastectomy
- Defined adequate baseline liver function with bilirubin and SGOT values instead of bilirubin alone, and added SGOT parameters to dose modification tables
- Changed separate randomization tables, one for Austrian sites and one for non-Austrian sites, into one central randomization
- Stratified by center as well as by number and site of metastases
- Changed mixing guidelines for cyclophosphamide
- Patients who achieved CR at cycle 5 needed to complete 6 cycles of chemotherapy, rather than 2 cycles beyond CR.
- Guidelines for radiation therapy were added (must have evaluable/measurable tumor outside the radiation port); previously not permitted
- Added LVEF assessment 2-4 months after stopping epirubicin therapy in all patients
- Patients evaluable for efficacy: defined as those patients who received at least 3 cycles with at least 4 follow-up assessments, unless there is rapid disease progression or death. Initially defined as 2 courses with 2 follow-up assessments
- The schedule of evaluations was changed.

At the time this amendment was made, 5 patients (3 on FEC 50 and 2 on FEC 100) had been randomized.

September 14, 1990

- Death on study, originally defined as only those deaths not due to disease progression, was expanded to include all deaths

Reviewer Comments:

1. The major protocol amendment occurred while few patients were on study. The timing of the amendment did not alter the study outcome.

2. The definition of patients evaluable for efficacy is too strict and is likely to exclude a significant number of patients from analysis.

3. The second protocol amendment was appropriate. All deaths should be considered in the study report and analysis.

12.5 Eligibility

12.5.1 Inclusion criteria

- Female patients with histologic proof of adenocarcinoma with Stage IV disease at diagnosis or recurrent disease, either locoregional or distant recurrence. Inflammatory breast cancer patients are not eligible. Patients with in-breast recurrence after lumpectomy are not eligible. Patients with locally advanced inoperable breast cancer are not eligible.
- Must not have received prior chemotherapy except for adjuvant therapy. Adjuvant therapy, if anthracycline-based, must have a cumulative dose of ≤ 60 mg/m^2 and patients must have been disease-free for at least 12 months
- Measurable and/or evaluable lesions located outside a prior radiation field
- > 18 years and < age 70
- May have received palliative radiation to no more than 25% of red bone marrow [Chart to calculate percentage of bone marrow included]
- Must report receptor status, if determined
- Must have recovered from the acute toxicities of prior chemotherapy or radiation therapy
- If patients received hormonal therapy, must be off therapy for at least 4 weeks and not demonstrate a withdrawal response
- PS ≤ 2
- Adequate hematologic, hepatic, and renal function
- LVEF measured by MUGA or ultrasound not more than 10% the normal lower limit of the institution

Reviewer Comments:

1. Patients with both measurable and evaluable disease were eligible. This inclusion criterion does not affect survival or TTP, but can make response assessment difficult.

12.5.2 Exclusion criteria

- Osteoblastic bone metastases and/or pleural or ascitic effusion as the only site of metastases
- Cardiovascular history of MI within the last year, clinical evidence of CHF or CAD, or arrhythmias requiring permanent medication or uncontrolled arterial hypertension
- ECG evidence of LVH, complete LBBB, complete RBBB plus left anterior hemiblock or left posterior hemiblock, coronary insufficiency (ST segment depression at rest), high risk uncontrolled arrhythmia (multifocal ventricular extrasystoles)
- History of malignancy other than localized basal or squamous cell skin carcinoma or non-invasive cervical carcinoma within 5 years of study entry
- Active infection
- Clinical evidence of brain metastases

12.6 Endpoints

12.6.1 As defined in the protocol

- Response was defined as follows:

CR: Complete regression of all evidence of tumor for at least 3 weeks. Whenever possible, CR was to be documented histologically.

PR: At least 50% decrease in the sum of the products of two longest perpendicular diameters of all measurable lesions, maintained for at least 3 weeks. No increase in the size of any tumor or appearance of any new lesion

NC: Less than 50% regression of measurable disease and less than 25% progression of measurable disease for at least 3 weeks. No new lesions must appear

PD: Greater than 25% increase in the sum of the products of two diameters of one or more measurable tumors or the appearance of new lesions.

Similar criteria were included for non-measurable disease as a general category. In addition, the following specific criteria were listed:

- Liver size could be used as a tumor measurement if there was evidence by scan or biopsy of liver disease and if the liver edge extended at least 5 cm below the costal margin or if there were radiographic defects. On scan, liver lesions were measurable if they were > 4 cm on liver scan or > 2 cm on ultrasound or CT scan.
- Bone metastases: criteria for response in bone were listed in the protocol. No change implied at least 6 weeks of stability. Fractures were not used as the sole indication of progressive disease.

Non-measurable and measurable disease were used together to determine response (published reference cited in the protocol). An independent reviewer evaluated all response assessments. In disagreements between the reviewer and the investigator, the reviewer's opinion was accepted unless the investigator supplied convincing evidence to document the differing opinion.

- Survival was defined as the time from initiation of drug therapy to death.
- Duration of response was defined as the time from the date the response was first recorded to the date progressive disease was first noted.
- Time to progression was defined as the time from the first day of treatment to the date of first observation of progressive disease.

12.6.2 As defined in the study report

- The best response was assigned by the independent reviewer.
- Duration of response was calculated from the date of the first documented response (for CR) or from the date of the first drug administration (for PR) to the first date of documented tumor progression.
- Time to response was defined as the interval in days elapsed between the date of randomization and the first date of best response (CR or PR).
- Time to progression was defined as the time in days between the date of randomization and the first date of documented progression or death due to any cause, whichever occurred first. Patients who were taken off study for refusal, toxicity, or loss to follow-up were censored at the last known date.
- Time to treatment failure was defined as the interval in days between the date of randomization and the date of failure. Failure was defined as disease progression, death, treatment discontinuation due to patient refusal, toxicity, or loss to follow-up. The date of failure was the first date of documented tumor progression or death or the last known date in the other cases.
- Survival was defined as the time in days from the date of randomization to the date of death or last known date.

Reviewer Comment:

1. Time intervals are usually measured from the date of randomization, which should be either identical or close to the date of treatment. This definition was used in the study report.

2. The study report (section 4.7.3, volume 2.44, page 028) lists definitions of measurability. These definitions were not included in the protocol document. The sponsor was asked about this point, and answered that this section was inserted erroneously into the study report. All lesions reported were used to evaluate response and progression.

3. Evaluable disease can be used to measure TTP, but it is difficult to include these patients in an evaluation of response rate.

4. Liver size is an unreliable way to measure hepatic involvement. The study report indicates that liver size was never used to assess response in this trial.

5. It is rare to observe an objective response in bone.

6. The study report included a table of overall response, based on measurable and non-measurable lesions. This table was not included in the original protocol.

7. The study report added the endpoints of time to response and time to treatment failure.

12.7 Statistical plan

12.7.1 Prospectively defined

The following assumptions were made in order to calculate sample size:

- Standard dose epirubicin in combination with cyclophosphamide and 5-FU results in a median survival of 18 months
- High-dose epirubicin will improve survival by 30%, to a median of 24 months
- Accrual time will be 24 months
- Data will be analyzed 30 months after completion of accrual
- Survival will be analyzed by the logrank test with a one-sided 5% significance level

It was calculated that 202 patients per treatment arm were required to detect this survival difference with 80% power.

For response rate, evaluable patients were those who completed at least 3 cycles of chemotherapy with at least 4 follow-up assessments, unless there was evidence of rapid disease progression or death earlier. Patients with early death were evaluable for toxicity and were considered non-responders. Patients who did not meet eligibility criteria or whose treatment deviated significantly from the protocol guidelines were considered inevaluable for response.

Toxicity evaluations were performed on patients who received 1 cycle of therapy. A course was defined as the period of drug treatment plus the time required for patients to recover from toxicity (about 3 weeks).

The statistical plan noted that the primary endpoint was survival time. Secondary endpoints were response rate, duration of response, TTP, RFS, and time to best response. Analyses were to be performed using the Kaplan-Meier method and groups were to be compared using the logrank test. Response rate, calculated as the ratio between the number of patients deemed to have CR + PR and all randomized patients, was to be calculated per arm and compared using the Chi-square test.

Reviewer Comments:

1. The survival assumptions used to calculate sample size were conservative.

2. The primary analyses should consist of intent-to-treat analyses. The sponsor's definitions of evaluable patients are likely to bias the results by selecting patients who remained on study longer, suggesting either increased response to and/or greater tolerance of therapy. The oncology literature reflects the fact that responders do better than non-responders, independent of the treatment selected.

3. All treated patients should be evaluable for toxicity, even if they did not complete an additional 3 weeks of follow-up.

12.7.2 As defined in the study report

12.7.2.a Patient characteristics

Patient characteristics (demographic data, receptor status, stage and histology at first diagnosis, prior therapy and baseline tumor characteristics) were summarized in frequency tables or with descriptive statistics. These analyses were performed on patients as randomized.

12.7.2.b Treatment and dose-intensity

Treatment was described as the maximum number of cycles administered, cycle duration, and dose intensity. Duration of each cycle was computed as the difference between the starting dates of two consecutive cycles. The last cycle was excluded from this analysis. Dose intensity, relative dose intensity, and average relative dose intensity were calculated as per Hryniuk et al. For each drug administered, the DI was calculated by adding the total dose of all cycles divided by the number of weeks from C1D1 to the date of the last cycle plus a fixed interval of 3 weeks. This dose was divided by the baseline BSA. The relative DI was calculated as the ratio between the DI of each drug delivered and the planned DI for each drug, and was expressed as a decimal fraction. For the drug combinations, the average relative DI was computed as the mean of the relative DI of the single components. Patients who received the randomized treatment were described in these analyses.

12.7.2.c Efficacy

Response rate was calculated for each arm as the ratio between the number of responders and the total number of patients in the analysis. This endpoint was calculated in patients with a diagnosis of breast cancer, and in patients who were eligible and evaluable for response. The response rates were compared with a Chi square test. An odds ratio with 95% CI was calculated.

OS, TTP, TTF, time to response, and duration of response were estimated with the Kaplan-Meier method; treatment arms were compared with the logrank and Wilcoxon tests. Hazard ratios with 95% CI were calculated. Overall survival was evaluated in the intent-to-treat population. The other parameters were evaluated in eligible patients evaluable for response. TTF was also analyzed in patients with a breast cancer diagnosis.

12.7.2.d Hematologic toxicity

Patients were evaluable for hematologic toxicity if at least 1 count was available between days 8 and 15 inclusive. For Hb, one evaluation per cycle was required to be evaluable. A patient was evaluable if she had at least one evaluable cycle. The worst nadir count was defined as the lowest value recorded during the cycle and during the treatment.

Patients were analyzed according to treatment actually received. The analysis was conducted on evaluable patients and evaluable cycles. An additional analysis was carried out on all treated patients and all cycles, in order to detect severe hematologic toxicity that may have occurred in non-evaluable patients or cycles.

Worst nadirs were presented in terms of descriptive statistics and were compared with a Chi-square test.

12.7.2.e Non-hematologic toxicity

Non-hematologic toxicity was expressed as WHO grade in patients according to treatment actually received. The frequency and percentage of WHO grades (worst grade) for each adverse event were summarized in frequency tables. Arms were compared with the Chi-square test for absent (grade 0), mild (grade 1-2), or severe (grade 3-4) toxicity. For adverse events that gave a significant difference, further analyses comparing grade 0 to any grade and comparing grade 1-2 versus grade 3-4 were performed and compared with a Chi-square test.

12.7.2.f Cardiac toxicity

For analysis of LVEF, patients were evaluable if a baseline value and at least 1 assessment with the same method were available. An event was defined as a decrease of the LVEF of $\geq$ 15% (absolute) relative to baseline, or $\geq$ 10% below the normal limit. All treated patients were evaluated for clinical cardiotoxicity (symptoms that required treatment interruption and decreased LVEF).

12.7.2.g Quality of life

The FLIC questionnaire was scored by adding the score of the individual items. For some items, the scoring was reversed so that a low score was always associated with a poor quality of life, and a high score was associated with a good quality of life. The items were structured to cover:

- Physical well-being and ability
- Psychological well-being
- Hardship due to cancer
- Social well-being
- Nausea

For missing values in areas 1 and 2, a prorated score was computed provided that the number of missing items was less than 50%. The prorated score was assigned as the mean score for all answered questions.

For areas 3-5, all questions had to be recorded in order to calculate the area scores.

An overall score was obtained by summing the subscale scores.

Because of poor compliance, no formal analysis was performed.

Reviewer Comments:

1. Overall survival was the primary endpoint, which should be analyzed on all patients as an intent-to-treat analysis.

2. Restriction of response rate evaluations to patients with breast cancer who are eligible and evaluable, as defined in the protocol, is likely to introduce bias.

3. Safety evaluations, as planned, were adequate.

4. Compliance with the QOL evaluations was poor and did not permit analysis of the data.